

This listing of claims replaces all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claim 1. (withdrawn) A construct comprising a metal ion-binding domain comprising two or more linked residues forming an  $N_3S_1$  ligand available for complexing with a metal ion, wherein the construct is conformationally constrained in a structure specific for one or more melanocortin receptors upon complexing the metal ion-binding domain with a metal ion.

Claim 2. (currently amended) A manufactured peptide and pharmaceutically acceptable salts thereof comprising a metal ion-binding domain comprising two or more contiguous amino acids and a ~~determined~~ biological-function domain specific for one or more melanocortin receptors and a metal ion complexed to the metal ion-binding domain, wherein at least a portion of said biological-function domain is co-extensive with at least a portion of the metal ion-binding domain, and wherein said biological-function domain is conformationally constrained upon complexing the metal ion-binding domain with a metal ion.

Claim 3. (withdrawn) A combinatorial library targeted to melanocortin receptors of different sequence peptide members synthesized on solid phase, where each constituent library member comprises:

(a) a peptide sequence of three or more amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues forming a metal ion-binding domain and including at least one amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues at the N- or C-terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain, and (iii) a cleavable bond attaching the peptide sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues in the peptide sequence of at least one of the constituent members of the library;

wherein the orthogonal S-protecting group may be removed without cleaving the peptide sequence from the solid phase.

Claim 4. (withdrawn) A combinatorial library targeted to melanocortin receptors of different sequence peptidomimetic members synthesized on solid phase, where each constituent library member comprises:

(a) a peptidomimetic sequence of a combination of three or more amino acid residues and mimics of amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding domain and including at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C- terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain, and (iii) a cleavable bond attaching the peptidomimetic sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof in the peptidomimetic sequence of at least one of the constituent members of the library;

wherein the orthogonal S-protecting group may be removed without cleaving the peptidomimetic sequence from the solid phase.

Claim 5. (withdrawn) A combinatorial library targeted to melanocortin receptors of different sequence peptide or peptidomimetic members synthesized in solution, where each constituent library member comprises:

(a) a peptidomimetic sequence of a combination of three or more amino acid residues and mimics of amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-

binding domain and including at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C- terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof in the peptidomimetic sequence of at least one of the constituent members of the library.

Claim 6. (canceled)

Claim 7. (currently amended) The ~~composition~~ peptide or salt thereof of claim 2 wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 8. (currently amended) The ~~composition~~ peptide or salt thereof of claim 2, wherein the composition is substantially more specific for one or more melanocortin receptors when the metal ion-binding domain is complexed with a metal ion than is the composition when the metal ion-binding domain amino-acid-sequence is not complexed with a metal ion.

Claim 9. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein the metal ion-binding domain further comprises at least one N available for binding to a metal ion upon removal of the orthogonal S-protecting group.

Claim 10. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein the metal ion-binding domain comprises three residues forming an N<sub>3</sub>S<sub>1</sub> ligand.

Claim 11. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein the orthogonal S-protecting group is S-thio-butyl, acetamidomethyl, 4-methoxytrityl, S-sulfonate or 3-nitro-2-pyridinesulfonyl.

Claim 12. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein the orthogonal S-protecting group may be removed from constituent library members thereof without otherwise altering the constituent library members or any amino acid side chain protecting group therein.

Claim 13. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein the structural diversity occurs in the metal ion-binding domain.

Claim 14. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein the structural diversity occurs outside the metal ion-binding domain.

Claim 15. (withdrawn) The combinatorial library of claim 3, 4 or 5 wherein one or more constituent library members include at least one amino acid residue or mimic of an amino acid residue in the sequence at the N- or C-terminus of the metal ion-binding domain containing at least one S wherein the said S is protected by a non-orthogonal S-protecting group, whereby the orthogonal S-protecting group may be removed without removing the non-orthogonal S-protecting group.

Claim 16. (withdrawn) The solid phase combinatorial library of claim 3 wherein the at least one amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine.

Claim 17. (withdrawn) The combinatorial library of claim 4 or 5 wherein the at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine; 3-mercapto phenylalanine; 2-mercaptoacetic acid; 3-mercaptopropionic acid; 2-mercaptopropionic acid; 3-mercapto-3,3,-dimethyl propionic acid; 3-mercapto-3,3,-diethyl propionic acid; 3-mercapto,3-methyl propionic acid; 2-mercapto,2-methyl acetic acid; 3-cyclopentamethylene,3-mercaptopropionic acid; or 2-cyclopentamethylene,2-mercaptoacetic acid.

Claim 18. (currently amended) The peptide of claim 2 of the formulas:

$R_1 - Lll - Aaa - Bbb - Ccc - R_2$ ,

$R_1 - Bbb - Aaa - Ccc - R_2$ ,

$R_1 - Ddd - Bbb - Aaa - R_3$ ,

$R_4 - Eee - Bbb - Ccc - R_2$ ,

$R_1 - Fff - Aaa - Ggg - Ccc - R_5$ ,

$R_1 - Hhh - Aaa - Bbb - Ccc - R_5$ , or

$R_1 - lll - lll - Ccc - Jjj - Kkk - R_2$ ,

wherein

$R_1$  comprises a functionality that potentiates the intrinsic activity of the remainder of the peptide molecule, including but not limited to providing an auxiliary or secondary receptor contact;

Aaa is an L- or D-configuration cationic amino acid with a positively charged side chain;

Bbb is an L- or D-configuration amino acid with an aromatic side chain;

Ccc is an amino acid that provides both a nitrogen atom (N), from the alpha amino group, and a sulfur atom (S), from a side chain group, for metal ion complexation;

Lll is a D-configuration amino acid with an aromatic side chain;

$R_2$  is optionally present, and if present, comprises an amino acid with an aromatic side chain;

Ddd is an amino acid that provides an S, from a side chain group, for metal ion complexation;

$R_3$  is an amino acid with an aromatic side chain that provides an N for metal ion complexation;

$R_4$  is a functionality that provides a cationic center;

Eee is an uncharged L- or D-configuration amino acid that provides an N for metal ion complexation;

Fff is an L- or D-configuration aromatic amino acid;

Ggg is an L- or D-configuration aromatic amino acid;

R<sub>5</sub> is an amide, substituted amide, ester or carboxylate group, or comprises an L- or D-configuration amino acid;

Hhh is an L- or D-configuration cationic amino acid with a positively charged side chain;

lil is an L- or D-configuration amino acid that provides an N for metal ion complexation;

Jjj is an L- or D-configuration amino acid with an aromatic side chain; and

Kkk is an L- or D-configuration cationic amino acid with a positively charged side chain.

Claim 19. (Withdrawn)                      The peptide of claim 18 of the formula R<sub>1</sub> – Lll – Aaa – Bbb – Ccc – R<sub>2</sub>, wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 20. (Currently Amended)                      The peptide of claim 18 of the formula R<sub>1</sub> – Bbb – Aaa – Ccc – R<sub>2</sub>, wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 21. (Withdrawn)                      The peptide of claim 18 of the formula R<sub>1</sub> – Ddd – Bbb – Aaa – R<sub>3</sub>, wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 22. (Withdrawn)                      The peptide of claim 18 of the formula R<sub>4</sub> – Eee – Bbb – Ccc – R<sub>2</sub>, wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 23. (Withdrawn)                      The peptide of claim 18 of the formula R<sub>1</sub> – Fff – Aaa – Ggg – Ccc – R<sub>5</sub>, wherein the metal ion-binding domain is complexed with a metal ion selected from the group

consisting of rhenium and technetium.

Claim 24. (Withdrawn)                      The peptide of claim 18 of the formula  $R_1 - Hhh - Aaa - Bbb - Ccc - R_5$ , wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 25. (Withdrawn)                      The peptide of claim 18 of the formula  $R_1 - Iii - Iii - Ccc - Jjj - Kkk - R_2$ , wherein the metal ion-binding domain is complexed with a metal ion selected from the group consisting of rhenium and technetium.

Claim 26. (Previously Presented)                      The peptide of claim 18 wherein  $R_1$  comprises an amino acid chain of from one to about four neutral or charged L- or D-configuration amino acid residues.

Claim 27. (Previously Presented)                      The peptide of claim 18 wherein  $R_1$  comprises a linear or branched alkyl, aryl, alkene, alkenyl, or aralkyl chain.

Claim 28. (Previously Presented)                      The peptide of claim 18 wherein Aaa is an L-configuration Lys, Arg, Orn, Dpr or Dbu, or derivative, analog or homolog thereof.

Claim 29. (Previously Presented)                      The peptide of claim 18 wherein Aaa provides an N for metal ion complexation.

Claim 30. (Previously Presented)                      The peptide of claim 18 wherein Bbb is a D-configuration Phe, Phe(4'-Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), or Tyr(BzlCl<sub>2</sub>), or derivative, analog or homolog thereof.

Claim 31. (Previously Presented)                      The peptide of claim 18 wherein the aromatic ring of the aromatic side chain of Bbb is substituted with one or more halogen, alkyl or aryl groups.

Claim 32. (Previously Presented)                      The peptide of claim 18 wherein Bbb provides an N for metal ion complexation.

Claim 33. (Previously Presented)      The peptide of claim 18 wherein Ccc is an L- or D-configuration Cys, Pen or Hcys.

Claim 34. (Withdrawn)      The peptide of claim 18 wherein Lll is a D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), or Tyr(BzlCl<sub>2</sub>), or derivative, analog or homolog thereof.

Claim 35. (Withdrawn)      The peptide of claim 18 wherein the aromatic ring of the aromatic side chain of Lll is substituted with one or more halogen, alkyl, or aryl groups.

Claim 36. (Withdrawn)      The peptide of claim 18 wherein Lll does not provide an N for metal ion complexation.

Claim 37. (Previously Presented)      The peptide of claim 18 wherein R<sub>2</sub> is an L- or D-configuration Phe, Trp, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr(BzlCl<sub>2</sub>), or derivative, analog or homolog thereof.

Claim 38. (Previously Presented)      The peptide of claim 18 wherein the C-terminus of R<sub>2</sub> is amidated.

Claim 39. (currently amended)      The peptide of claim 18 wherein R<sub>2</sub> is a des-carboxyl amino acid corresponding to ~~any of the L- or D-amino acid residues of claim 37~~ an L- or D-configuration Phe, Trp, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr(BzlCl<sub>2</sub>) .

Claim 40. (Previously Presented)      The peptide of claim 18 wherein R<sub>2</sub> is absent.

Claim 41. (Withdrawn)      The peptide of claim 18 wherein Ddd is an L- or D-configuration Cys, Pen or Hcys.



Claim 42. (Withdrawn)                      The peptide of claim 18 wherein R<sub>3</sub> is an L- or D-configuration Phe, Trp, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr(BzlCl<sub>2</sub>), or derivative, analog or homolog thereof.

Claim 43. (Withdrawn)                      The peptide of claim 18 wherein the C-terminus of R<sub>3</sub> is amidated.

Claim 44. (Withdrawn)                      The peptide of claim 18 wherein R<sub>3</sub> is a des-carboxyl amino acid corresponding to any of the L- or D-amino acid residues of claim 42.

Claim 45. (Withdrawn)                      The peptide of claim 18 wherein R<sub>4</sub> is an L- or D- configuration Lys, Arg, Orn, Dpr or Dbu, or derivative, analog or homolog thereof.

Claim 46. (Withdrawn)                      The peptide of claim 18 wherein the N-terminus of R<sub>4</sub> is functionalized with a neutral amino acid or non-peptide group comprising a linear or branched alkyl, aryl, alkene, alkenyl or aralkyl chain.

Claim 47. (Withdrawn)                      The peptide of claim 18 wherein Eee is an Gly or an L- configuration Ala, Nle, Leu, Val, Phe or Trp, or derivative, analog or homolog thereof.

Claim 48. (Withdrawn)                      The peptide of claim 18 wherein Eee is an amino acid with an aliphatic side chain.

Claim 49. (Withdrawn)                      The peptide of claim 18 wherein Fff is a D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), Tyr(BzlCl<sub>2</sub>), Tic, Tiq or Tca, or derivative, analog or homolog thereof.

Claim 50. (Withdrawn)                      The peptide of claim 18 wherein the aromatic ring of the aromatic side chain of Fff is substituted with halogen, alkyl or aryl groups.

Claim 51. (Withdrawn)                      The peptide of claim 18 wherein Fff does not provide an N for metal ion complexation.

Claim 52. (Withdrawn)                      The peptide of claim 18 wherein Ggg is an L-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal, Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl) or Tyr(BzlCl<sub>2</sub>), and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids.

Claim 53. (Withdrawn)                      The peptide of claim 18 wherein the aromatic ring of the aromatic side chain of Ggg may be substituted with halogen, alkyl or aryl groups.

Claim 54. (Withdrawn)                      The peptide of claim 18 wherein Ggg provides an N for metal ion complexation.

Claim 55. (Withdrawn)                      The peptide of claim 18 wherein R<sub>5</sub> is an L- or D-configuration aromatic, aliphatic, neutral or charged amino acid, optionally further comprising an amide group.

Claim 56. (Withdrawn)                      The peptide of claim 18 wherein Hhh is an L-configuration Lys, Arg, Orn, Dpr or Dbu, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids.

Claim 57. (Withdrawn)                      The peptide of claim 18 wherein Hhh does not provide an N for metal ion complexation.

Claim 58. (Withdrawn)                      The peptide of claim 18 wherein Iii is an Ala, Gly, Nle, Val, Leu, Ile, His, Lys, or Arg, and derivatives, analogs or homologs thereof, including both natural and synthetic amino acids.

Claim 59. (Withdrawn)                      The peptide of claim 18 wherein Jjj is a D-configuration Phe, Phe(4'Cl), Phe(3',4' Di-Cl), Phe(4'-nitro), Phe(4'-methyl), Phe(4'-Phenyl), Hphe, Pgl, Trp, 1-Nal, 2-Nal,

Ser(Bzl), Lys(Z), Lys(Z-2'Br), Lys(Bz), Thr(Bzl), Cys(Bzl), or Tyr(BzlCl<sub>2</sub>), and derivatives, analogs or homologs thereof.

Claim 60. (Withdrawn)                      The peptide of claim 18 wherein the aromatic ring of the aromatic side chain of Jjj is substituted with one or more halogen, alkyl or aryl groups.

Claim 61. (Withdrawn)                      The peptide of claim 18 wherein Jjj does not provide an N for metal ion complexation.

Claim 62. (Withdrawn)                      The peptide of claim 18 wherein Kkk is an L-configuration Lys, Arg, Orn, Dpr or Dbu, or derivative, analog or homolog thereof.

Claim 63. (Withdrawn)                      The peptide of claim 18 wherein Kkk does not provide an N for metal ion complexation.